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Relationships between Magnesium and Protein Concentrations in Serum

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We determined concentrations of magnesium, total protein, albumin, and globulin in more than 74 000 serum specimens from patients and noted a direct linear relationship between the concentration of magnesium in serum and the concentrations of total protein, albumin, and globulin in serum. Albumin and magnesium concentrations are linearly related at high and low albumin concentrations; within the reference interval, however, the magnesium concentration is independent of the albumin concentration. Linear regression analysis suggests that 25% of the total serum magnesium is bound to albumin and 8% to globulins.

Additional Keyphrases: *albumin · globulins · variation, source of · binding of Mg^{2+} to plasma proteins · distribution of values for plasma proteins in a population*

Magnesium is the second most abundant divalent cation in serum, exceeded only by calcium. Approximately 1% of the total body magnesium is extracellular, its intracellular concentration being significantly higher than that in serum (*1–3*). The serum concentration is quite constant in healthy people, but studies have reported mean population values ranging from 0.62 to 1.07 mmol/L (*1*). Different populations and methodologies for the determination of magnesium probably contribute to the width of this range (*2*). Approximately 30% of serum magnesium is bound to protein, primarily albumin, possibly at the same site as serum calcium (*1, 4*), but in lesser percentages than calcium. Several algorithms have been developed to account for the serum protein concentration in adjusting the total serum calcium concentration, but there are no similar algorithms for magnesium.

The distribution of values for the magnesium concentration in the serum of normal people is gaussian (*5*). In hospitalized patients, however, it is nongaussian and shows a broader range of values than in healthy people (*6*). The effect of the concentration of serum proteins on the total magnesium concentration in serum may be analogous to the effect of the concentration of serum proteins on the total concentration of calcium. We chose to examine the variation in the concentration of magnesium as a function of albumin, globulin, total protein, and albumin/globulin ratio to see whether correlations exist.

Materials and Methods

We investigated the relationships between concomitantly determined concentrations of magnesium and (*a*) albumin in 90 017 specimens, (*b*) total protein in 83 912 specimens, and (*c*) globulin in 74 593 specimens from patients at the Clinical Center of the National Institutes of Health. The results presented here are from determinations performed on specimens received and analyzed between 1975 and 1983. Magnesium was determined by atomic absorption spectroscopy (Perkin-Elmer Corp., Norwalk, CT 06856). Albumin was determined by continuous-flow analysis (SMAC; Technicon Instruments Corp., Tarrytown, NY 10591) by the bromcresol green dye-binding method. Total protein concentration was determined by the SMAC biuret method. The globulin concentration was calculated as the remainder after subtracting albumin from total protein.

For our analysis, we assessed the magnesium concentration in serum samples containing 25 different albumin concentrations, ranging from 26 to 50 g/L, in 1 g/L increments. The number of specimens in each increment ranged from 319 to 6991; this distribution (Figure 1) is nongaussian, with a mean of 3600. We calculated the mean and standard error of magnesium concentration for each incremental albumin concentration. We divided the albumin concentrations into three sections, 26 to 39 g/L, 39 to 45 g/L, and 45 to 50 g/L, and performed a linear-regression analysis on the relationship of mean magnesium concentration to albumin concentration in each section (Table 1 and Figure 1). Similar analyses were performed for total protein (range 45–65 g/L) and globulin (range 20–35 g/L) concentrations and the albumin/globulin ratio.

Results and Discussion

Albumin and magnesium are linearly related at concentrations of albumin ranging from 45 to 50 g/L (high albumin range) and 26 to 39 g/L (low albumin range). A plateau of the mean concentration of magnesium was evident in the range of 39 to 45 g of albumin per liter (intermediate range). For this plateau region the correlation coefficient is −0.09, implying that magnesium concentration is independent of albumin concentration.

The *y*-intercept represents the theoretical value for magnesium concentration at a zero albumin concentration: this value, which can be used to estimate non-albumin-bound magnesium in serum, is 0.615 mmol/L. The fraction of magnesium bound by albumin may be estimated from the following formula:

$$\text{Percentage bound} = \frac{\text{mean }[Mg^{2+}] - (y\text{-intercept})}{\text{mean }[Mg^{2+}]} \times 100$$

We estimate that 25% of magnesium is bound by albumin. Applying this same formula to the other protein categories, we find that 8% of the magnesium is bound to globulin, 32% to total protein. Thus, of the magnesium bound to protein, about three-fourths is bound to albumin and the rest to globulin. The percentage of magnesium bound to these two protein fractions is independent of their ratio in serum (Figure 1). A formula for correction of magnesium concentration as a function of albumin concentrations below the reference interval is therefore:

$$Mg_C^{2+} = Mg_T^{2+} + 0.005(40 - \text{Alb})$$

where Mg_C^{2+} is the corrected magnesium concentration (mmol/L), Mg_T^{2+} is the total or experimentally determined magnesium concentration (mmol/L), and Alb is the concentration of albumin in g/L. For example, if the concentration of albumin in serum is 20 g/L and the measured magnesium

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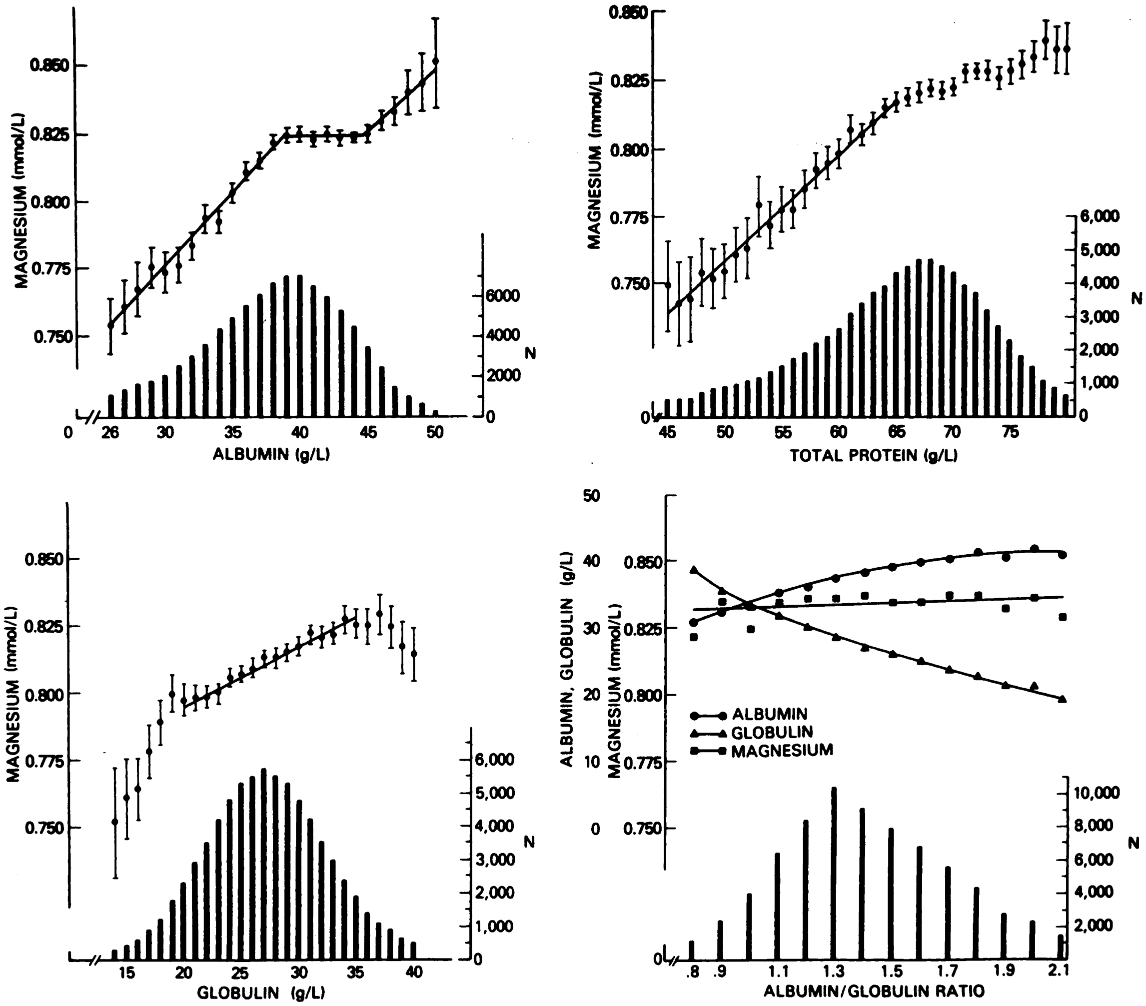

Fig. 1. Distribution of magnesium concentrations (mean ± 2 SEM) in sera with various protein contents

Upper left: Serum magnesium vs incremental concentrations of serum albumin, as analyzed by linear regression for three albumin regions: low (26–39 g/L), intermediate (39–45 g/L), and high (45–50 g/L). The number of specimens for each increment of albumin concentration is shown in the bar graph. *Lower left:* Serum magnesium vs incremental concentrations of serum globulins. *Upper right:* Serum magnesium vs incremental concentrations of total serum protein. *Lower right:* Magnesium, albumin, and globulins vs increments of the albumin/globulin ratio

Table 1. Regression Results for Magnesium (y) and Serum Proteins (x)

Protein concn range, g/L	n	Slope × 10^3 [a]	y-intercept [b]	$S_{y \cdot x} \times 10^3$	r
Albumin					
26–39	14	5.35 ± 0.21	0.616 ± 0.007	3.21	0.991
39–45	7	−0.036 ± 0.177	0.826 ± 0.007	0.94	−0.090
45–50	6	5.19 ± 0.32	0.591 ± 0.015	1.33	0.993
Globulin					
20–35	16	2.12 ± 0.09	0.754 ± 0.002	1.63	0.988
Total protein					
45–65	21	3.90 ± 0.14	0.565 ± 0.008	3.89	0.988

[a] Slope ± SE: Mg^{2+}, mmol/g of protein.
[b] y-intercept ± SE: Mg^{2+}, mmol/L.

is 0.7 mmol/L, the magnesium concentration corrected for the low albumin would be 0.8 mmol/L [0.8 = 0.7 + 0.005 (40−20)]. This formula may be useful for adjusting the concentration of magnesium to account for variation in the concentration of albumin in the serum of hospitalized patients.

The percentage of magnesium bound to serum proteins noted in this study is consistent with results of previous studies involving ultrafiltration of serum. One of the earliest studies on this topic, by Walser (*7*), reported 32% of magnesium bound to serum proteins. In his review of magnesium metabolism, Walser (*1*) cites 15 references for the percentage of ultrafilterable (nonprotein bound) magnesium in serum, with a mean value of 70% (i.e., 30% bound to protein) and a range of 55 to 85%. Recently, Speich et al. (*5*) obtained an ultrafiltrate of serum by ultracentrifugation and found 33.7% of the serum magnesium in males bound to protein and 32.9% bound in females. Our study extends the results of previous ones, because we estimate the percentage of magnesium bound to the two serum protein fractions, albumin and globulins, in addition to the total protein-bound concentrations.

Knowledge of the specific magnesium-binding proteins in the globulin fraction is important, because globulin proteins are frequently elevated or depressed in disease. The current study indicates that about one-fourth of the bound magnesium is attached to globulins. In vitro studies by Prasad et al. (*4*) showed binding of magnesium by alpha- and beta-globulins but not gamma-globulins (*4*). Further studies are needed to characterize the binding of magnesium among the globulin fractions.

What accounts for the plateau in the relationship between albumin and magnesium? The plateau occurs within the reference interval for albumin, which represents the vast majority of patients and normal individuals. These data suggest that factors other than albumin, perhaps renal and (or) hormonal, are stabilizing the magnesium concentration. Clearly the primary factor controlling the serum concentration of magnesium is the kidney (*8, 9*). The primary site of modifications of magnesium reabsorption is in the thick ascending limb of the Henle's loop, and magnesium transport at this level is largely affected by the concentrations of magnesium and calcium in plasma (*8*). No specific hormonal controls regulating magnesium transport have as yet been identified, though parathyrin seems to enhance magnesium reabsorption in the loop of Henle and the distal convoluted tubule (*8*).

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